REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1-9, 12-17, 19-33, 35-38 and 42-78 are in the case and are before the Examiner.

I. The Amendments

Claims 1 and 63 have been amended pursuant to the Examiner's helpful suggestion. Those amendments further clarify that the "5 residues from position 135 to the HBc terminus" are HBc residues 136-140 by insertion of the phrase "through position 140 toward" after "position 135" with cancellation of the word "to". Support in the specification can be found in several places including at least at page 25, second sentence of the second paragraph; page 39, third sentence of the bridging paragraph; and page 44, first sentence of the bridging paragraph with page 45. Claims 18 and 75 have been amended in parallel to recite that Domain IV contains "5 through fourteen" residues from position 135 through position 149. Specific support can again be found through out the specification, but particularly in original claims 42, 78 and 82. Claim 63 has also been amended to recite "5" residues instead of the inadvertently written six residues.

The first subparagraph of claim 51 has been amended to clarify that the one or more immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus is a "heterologous" epitope. Support for this amendment can also be

found through out the application text. Particular support is found at least in the full paragraph of page 26.

• Claim 70 was amended to improve the antecedent basis for its limitation pursuant to the Examiner's helpful observation.

It is thus seen that no new matter has been added.

II. The Action

A. Rejections Under 35 USC §112, Second Paragraph

The Action has asserted that the claims are "replete" with ambiguities and are other wise indefinite for several reasons. These bases for rejection are taken up below in the order of their appearance in the Action and are respectfully traversed.

(1) "conservatively substituted"

The independent claims except for claim 51 use the term "conservatively substituted", and there is a definition of that phrase on page 18. The gist of this portion of the rejection appears to be that when the percentage of allowable substitutions or numbers of substituting residues in an HBc sequence is discussed at pages 47-48 in regard to how to treat deletions, the person of skill in this art to whom the invention is directed was instructed to deem a deletion as a conservative substitution.

Once the context surrounding that discussion is read completely and that text is understood to be for the purpose of

calculating the percentage or number of allowable substitutions, there is neither inconsistency nor is there indefiniteness. Furthermore, inasmuch as a patentee can be his own lexicographer, the applicant is free to further define his definition of a "conservative substitution" in that it is not misleading, and is trivially straight forward. As such, this basis for rejection should be withdrawn.

(2) Sequence Comparison

The Action continued by asserting a lack of clarity as to which sequence one uses to determine a conservative substitution. This assertion lacks merit in that several mammalian HBc sequences are disclosed and can be used, and the plain language of the text is clear to a skilled worker. It appears as though the Action is really trying to assert a breadth rejection in the guise of alleged indefiniteness, but breadth is not indefiniteness. *In re Gardner*, 166 USPQ 138 (CCPA 1970).

It is agreed that the subtype *ayw* sequence shown in Fig. 7 (SEQ ID NO:247), is preferred. On the other hand, the other human subtype sequences can be used as can a sequence from another mammal. The Examiner's attention on this point is invited to the paragraph bridging pages 22 and 23. Examination of Fig. 7 illustrates the similarities between the several sequences and use of any would be no problem to a skilled worker. In addition, should a worker choose to use residues of positions 1-80 of one sequence linked to the residues of positions 81-149 or 156 of another sequence, as indicated in the allegedly vague disclosure, even a non-skilled worker would be

able to determine that fact by simply looking at the sequences of Fig. 7. Once the originating HBc sequence was determined, that worker could also determine the number of non-HBc residues were present.

The Action next complains that sequence selection in regard to substitutions is dependent upon whether truncations are present. The claims recite that substitutions are based upon the "HBc sequence". Thus, claims such as claim 1 state "chimer molecules (i) containing no more than 20 percent conservatively substituted amino acid residues in the HBc sequence". This being the case, one must take truncations in to account because a contemplated chimer can contain one or more added epitopes, most of whose would likely be deemed substitution s relative to the HBc sequence.

It is thus submitted that this basis for rejection should also be withdrawn.

(3) "5 residues from HBc position 135 to the HBc terminus"

Although it is believed clear as written, claims 1, 18, 63 and 75 have been amended to further clarify that the "5 residues from position 135 to the HBc terminus" are residues 136-140 by insertion of the phrase "through position 140 toward" after "position 135" with cancellation of the word "to", or by use of "5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III". The Examiner is thanked for noting this apparent lack of clarity, and it is believed that this basis for rejection is moot.

(d) "Domain IV contains zero through fourteen residues of a HBc ..."

Claims 18, 42, 63, 75, and 78 were said to be vague and indefinite because of their inclusion Domain IV contains zero through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III..." Claims 18, 63 and 75 have been amended to over come this point of apparent ambiguity. It is submitted, however, that claims 42 and 78 included the sequence of five residues fro position 136 to which the other claims were amended so this point is not believed to have been applicable to all five of the claims recited. It is also reiterated that these claims recite that the residues are "of a HBc amino acid residue sequence from position 136..." so that is should be clear that the recited residues are at least those of an HBc sequence from positions 136, 137, 138, 139 and 140. It is thus believed that this basis for rejection is moot.

(4) "heterologous linker residue..."

The Action asked how one could tell whether a residue were "heterologous", especially when one allows for conservative substitutions within the HBc sequence. The Action also asserts that the immunodominant loop contains "numerous residues that could be used as linker residues. Why then would one want to add additional linker residues?" This basis for rejection is traversed for several reasons.

It is first very easy for one skilled in the art to whom the invention is directed to determine whether a given

residue is "heterologous" or not. All that that person need to do is look at a sequence in Fig. 7. If that person needs to know what a "conservative substitution" is, perhaps he or she should read the specification as discussed previously at page 18.

In regard to the above-quoted portion of the Action, the Examiner's attention is invited first to the paragraph bridging pages 39 and 40 of the subject application at which place linkers are discussed. The Examiner's attention is thereafter invited to PCT/US99/03055 or its issued US counterpart, US Patent No. 6,231,864 B1 that is document A6 of the IDS. As will be seen from the disclosure in the issued patent, at column 3, lines 46-59, and particularly at lines 54-56, "the native, unmodified hepatitis B core protein particle does not exhibit appreciable chemical reactivity of the amino acid side chains in the native sequence." There is thus an art-recognized need for why one would want to add additional linker residues. It is thus submitted that there is no indefiniteness here, and this basis for rejection should be withdrawn.

(5) "of at least about"
and "up to about"

Claims 1, 18, 28, 63 and 68 were asserted to be indefinite because of their use of one or the other of "of at least about" and "up to about". It cannot be agreed that the use of "of at least about" made either of claims 1 and 63 that contained that phrase indefinite, nor can it be agreed that the use of the phrase "up to about" made any of claims 18, 28 or 68 indefinite.

Attached Exhibit 1 is a copy of a search made by the undersigned of the US Patent Office data base in which presumptively valid US patents with claims that contain the phrase "at least about" were sought, whereas attached Exhibit 2 is a similar search result in the US patent Office data base in which the presence of the complained of phrase "up to about" in issued US patent claims was assayed. As is seen from the attached, more than almost 60,000 presumptively valid US patents have issued since 1976 that contain one or more claims that include the phrase "at least about", whereas more than 23,000 presumptively valid US patents have issued since 1976 that contain claims that include the complained of phrase. It is respectfully submitted that the phraseology of issued patent claims is prime facie evidence of language that is not indefinite, and as such, this basis for rejection should be withdrawn.

(6) Claims 18 and 19

Claim 18 recites three locations for the possible inclusion of a heterologous epitope. Those locations are in Domains I, II and IV, as is seen from the quoted portions below:

> (a) Domain I comprises ... and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;
>
> (b) Domain II comprises ... one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope ...;

> (d) Domain IV comprises ... (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, ...

Claim 19 recites that the "recombinant HBc chimer protein molecule according to claim 18 that contains two heterologous epitopes." Thus, two of the three possible positions of the chimer of claim 18 contain a heterologous epitope. As such, both the statement of the Action beginning "[w]here claim 18 contains..." and the question that begins "[o]r does applicant mean..." are both incorrect and the claims are perfectly clear to a worker of ordinary skill. As such, it is submitted that this basis for rejection should be withdrawn.

(7) Claims 63 and 66

The Action, at the bottom of numbered page 5, states that "[c]laim 66 recites the limitation a second heterologous epitope in reference to claim 63." Examination of counsel's copy of the claims, indicates that perhaps claim 69 was intended by the Action rather than claim 66. Indeed, claim 69 recites the "immunogenic particle according to claim 63 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc." The remainder of this portion of this Reply will presume that claim 69 was inadvertently typed as 66.

The Examiner's attention is invited to US Patent No. 3,959,322, attached as Exhibit 3, and particularly to claims 1, and 2 through 8. It is there seen that claim 1 recites nothing about a substituent at position 17, whereas claims 2-8 recite substituent groups at that 17-position. It is submitted that

claims 63 and 69 herein are similar in construction in regard to antecedents. It is also noted that the attached '322 patent was the subject of *Ortho Pharmaceutical v. Smith*, 22 USPQ2d 1119 (Fed. Cir. 1992), wherein the claims were held valid.

(8) Claim 70

Claim 70 was said to have insufficient antecedent basis to recite "said B cell epitope". The Examiner is thanked for noting that inadvertent error. Claim 70 has been amended to depend from claim 67 rather than 68. Claim 67 recites that the "heterologous epitope is a B cell epitope." It is thus submitted that this basis for rejection is moot.

B. Rejections Under 35 USC §102(b)

1. Zlotnick et al.

(a) Claims 1, 12-18, 36-38, 51-60, 63-65 and 68-71

Claims 1, 12-18, 36-38, 51-60, 63-65 and 68-71 were rejected as allegedly anticipated by the disclosures of the paper by Zlotnick et al. (hereinafter Zlotnick) that was document A29 of the IDS. The Action has tried to characterize the Zlotnick disclosures in terms of the present claims, and has failed to appreciate what it is that Zlotnick has disclosed. As such this basis for rejection is respectfully traversed.

Zlotnick made three HBc-like sequences. Those materials are shown schematically in Fig. 1a at the top of page 9557. From the top down, the first is native HBc that was made by other than Zlotnick. The next construct, identified as

Cp149, was C-terminally truncated to position 149 and contained the cysteines at their native positions of 48, 61 and 107. The second "new" construct is identified as Cp*149 that contains an alanine, "A", in place of each of the above-noted cysteines, and was similarly C-terminally truncated. The third "new" construct was denominated Cp*150. That construct was similarly C-terminally truncated and had the same three alanines replacing the three internal cysteines, as well as an added cysteine at residue position 150. The last construct included the protamine sequence from position 150 through position 183 and is not germane to this discussion.

Thus, only construct Cp*150 contained a C-terminal cysteine, but that structure had non-conservative substitutions of alanine for cysteine, and neither an added linker for an epitope, an epitope or deletions in the immunodominant loop. Thus, none of the Zlotnick structures anticipates what is claimed here.

The properties of that Zlotnick construct provide no insight nor suggestion about another construct, such as that claimed herein that contains an insert. Indeed, the Schodel papers discussed in the paragraph bridging pages 6 and 7 of the specification note the instability observed with C-terminally-truncated HBc proteins that contain insertions in their sequences as is claimed herein. Thus, the import of the heterologous residues whose presence is neither shown nor suggested by Zlotnick is that such residues are known in the art to cause instability.

As noted previously, the art knew that HBc with its otherwise native linker residues was a poor bonder with added

antigens so there was an art-recognized need for additional linker residues. To proclaim that other residues are available to serve a linker function only admits a lack of ordinary knowledge in this field. This basis for rejection should be withdrawn.

(b) Claims 51-60

Claims 51-60 were rejected as allegedly anticipated by the disclosures of Zlotnick. This basis for rejection is respectfully traversed. The deficiencies of the Zlotnick disclosure as applied to the present claims were noted previously and are incorporated herein by reference. Those deficiencies include the lack of any additional heterologous immunogenic sequence(s), whose presence in the claimed subject matter has been highlighted by the present amendment. This basis for rejection should be withdrawn, as should Zlotnick as a reference against the claims.

2. Ireland et al.

Claims 1-8, 18, 27-28, 32-33, 42, 63 and 75 were rejected as allegedly anticipated by the disclosures of Ireland et al. US Patent No. 5,990,085 (hereinafter Ireland). That patent teaches the insertion of a peptide sequence from the inhibin molecule into the HBc molecule at one of two positions. The first is at position 144 of a truncated HBc whose C-terminal final HBc residue is at position 144, whereas the other construct places the inhibin peptide within the sequence of full-length core at position 78.

The Action noted that the Ireland construct having an insert at position 78 was also truncated after position 144. The Borisova et al. *Intervirology* **39**:16-22 (1996) article disclosed the original preparation of the plasmid (p2-19) from which the chimera was prepared. That article was cited in the Ireland patent at column 3, lines 61-64, and is attached as Exhibit 4 for the Examiner's convenience. Another article that discussed vectors for making constructs with insertion after position 144 [Borisova et al., *FEBS Letters* **259(1)**:121-124 (1989)] that was noted at column 3, lines 54-61 is attached as Exhibit 4A for the Examiner's convenience. Both of these papers are listed on enclosed Form PTO 1449. The Examiner's attention is invited to Fig. 2 on page 19 of Exhibit 4, and particularly to the "polylinker sequences" nucleic acid illustrated at positions 77-78 and 144 of vectors pII-116 and p-1-19.

The Action added the unnecessary disclosure of Zhou et al. for the fact that HBc naturally contains a cysteine residue at position 107. That disclosure was unnecessary because Fig. 7 of this application shows the location of the native Cys residues and Zlotnick noted the positions of the Cys residues in the previously relied-on paper. The Action then asserted that an Ireland chimer C-terminally truncated at position 144 having a cysteine at position 107 "satisfies a limitation" of a claimed chimer because the Cys residue at position 107 that was 37 residues toward the N-terminus from the C-terminal HBc residue was "about 30 residues from the C-terminus of the chimer molecule"

Unfortunately, this portion of the Action quoted the claim language out of context and missed a point of a limitation of the claim. The pertinent part of claim 1 reads:

> (b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule...(emphasis supplied)

Thus, the actually claimed subject matter requires that the cysteine referred to be both "toward the C-terminus from the C-terminal residue of the HBc sequence", and about 30 residues from the C-terminus of the molecule, rather than toward the N-terminus from the C-terminal residue of the HBc sequence and about 30 residues from the C-terminus of the molecule. Inasmuch as the whole basis for this part of the rejection is based on a mischaracterization of the claim, this basis for rejection should be withdrawn as should Ireland as a reference against the claims.

C. Rejection Under 35 USC §103(a)

(1) Pumpens In View Of Zlotnick

(a) First Rejection

Claims 1-9, 12-33, 35-38, 42-78 were rejected as allegedly obvious over the disclosures of Pumpens et al. (1995), hereinafter Pumpens, in view of Zlotnick, noted previously. This rejection is respectfully traversed.

The Action discussed the Pumpens report of chimeras that contain a heterologous epitope discussed in Table 1 of Pumpens. Unfortunately, Table 1 of the Pumpens paper relates to "full length" chimeras of HBc, not truncated chimeras. This is seen by the title of the Table that includes the words "full length".

The Action continued by reference to Pumpens at page 69, last paragraph, for a disclosure of "a heterologous linker residue for a conjugated epitope present in the HBC (sic) immunodominant loop." Unfortunately again, the "linker" discussed by Pumpens is the same type of "linker sequence" discussed in Borisova of Exhibit 4. That linker sequence is otherwise known as a polylinker, which is a nucleotide sequence that contains one or more recognition sites for restriction endonucleases as are shown in Fig. 2 of the Borisova paper of Exhibit 4 in the regions coding for HBc positions 77-78 and after 144, respectively. It is respectively submitted that this rejection that is premised on two such gross mischaracterizations should be withdrawn.

The Action continued with its discussion of the Pumpens disclosures to point out that Pumpens notes that "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." That statement was echoed by the later-published Borisova paper of Exhibit 4 that states near the top of the right-hand column of page 18 "HBcΔ (C-terminally-truncated HBc particles) were less stable than the corresponding full-length protein particles."

The Action also noted that Pumpens asserted that foreign insertions internal to the sequence "also exert an stabilizing effect on chimeric HBCΔ (sic) derivatives." The Action left out the basis for that statement, which was a parenthesized citation to unpublished results of Borisova. Interestingly, the Borisova paper of Exhibit 4 was published after the Pumpens paper and dealt with such internal insertions into HBc, but reported no enhancement of stability. Thus, Borisova had an opportunity to report on the alleged enhanced stability and did not do so. That tends to negate the comment from unpublished results.

On the other hand, the present inventor asserts a lessening of stability with truncated HBc chimers that contain inserts that lack a C-terminal cysteine. His application has actual data in the examples that illustrate that instability, and further illustrate added stability for an otherwise identical chimer when a C-terminal cysteine is present. One skilled in the art would favor real data over a reference to unpublished results, particularly in view of the fact that the cited author of those unpublished results published on the underlying technology and made no mention of the alleged result.

The Action asserts that Zlotnick teaches that addition of a cysteine provided a stabilizing effect with two page citations. Thus, Zlotnick teaches in the Summary at page 9556 that addition of gold particles to an engineered mutant assembly domain provided a labeled protein unimpaired in its ability to form capsids. This construct was described in the text near the bottom of the right hand column of page 9556 just above "MATERIALS AND METHODS" was noted to have the three internal

cysteines replaced by alanines and a new cysteine added at position 150. That construct was also referenced to Fig. 1a, as discussed previously.

The disclosure at page 9558 was somewhat more expansive, but still lacking as it was applied to the present claims. There, the same internal cysteine-lacking protein construct (Cp*150) with and with out gold was said to form capsids. The oxidized form of the cysteines was said to form oxidized disulfide-bonded dimers and the disulfides so formed stabilize the quaternary structure of the capsids. Of course, that comparison was made with the Cp*149 construct that had no cysteines at all. However, this disclosure says nothing about the effect of a C-terminal cysteine on a truncated HBc molecule that has its internal cysteines nor such a molecule that has an inserted sequence.

The Action concluded this section by asserting that Zlotnick has residues that could be used as linkers for a conjugated epitope. The problem here is that none of those so-called linkers in the native sequence had been shown to be effective, and a skilled worker would have known that. Thus, all that remains is an unsupported assertion that should be backed by art or an affidavit as are required under §1.104(d).

The Action concluded that a worker of ordinary skill would be motivated to combine the above teachings to arrive at the claimed subject matter. This conclusion also cannot be agreed with, even if the relied-on disclosures were as stated. Because the disclosures have been so misconstrued and misstated, the conclusion reached in the Action is still further from propriety. As was already noted, the sidebar assertion of

Pumpens upon which so much weight is placed that sequence insertions cause HBc chimer particle stabilization is unsubstantiated by the one to whom it was ascribed, Borisova, who had the opportunity and said nothing when he published thereafter on the same technology. Those assertions are further undermined by the sworn real data of the application that show a completely contrary result.

If one believed the unsubstantiated assertion of Pumpens, there would be no reason to add the C-terminal cysteines of Zlotnick by combining those teachings. Contrarily, the problem of instability would have been solved by inserting foreign sequences if Pumpens were correct. Of course, had the instability problem been solved as suggested by the Action or as suggested by Pumpens, the problem alluded to in the application at page 7 and noted in Ulrich et al., *Adv. Virus Res.*, vol.50 (1998) Academic Press pages 141-182 (IDS document 28), concerning "the requirement of reproducible preparation of intact chimer particles that can also withstand long-term storage" would have been met and Ulrich, writing three years after Pumpens, would have been mistaken.

Alternatively, if the skilled worker followed the usual procedure exhibited by workers of ordinary skill in science, and gave more credence to the later-published article of Ulrich over the earlier-published article of Pumpens that is cited in Ulrich, that worker would know that the problem of stability was not solved by inserting a heterologous sequence into the HBc sequence. Ulrich also cited the relied-on Zlotnick publication, and not having the present invention laid out before him did not suggest that stability could be achieved by

combining those teachings. It is again submitted that this basis for rejection should be withdrawn.

b) Second Rejection

Claims 1, 2, 9, 12-18, 24, 32, 33, 36-38, 42, 45, 51-60, 63-66, 68-71, 75 and 78 were rejected over the combined teachings of Pumpens in view of Zlotnick. The Action repeats the Pumpens teaching of heterologous epitopes and restates the erroneous assertion concerning linker residues. A further reference to Table 2 of Pumpens at page 67 for linker residues, however, none is seen in the table whose contents are said to relate to "internally inserted epitopes". Thus, again, this basis for rejection should be withdrawn because it is based on erroneous interpretations of the art that one skilled in this art would not make.

(2) Thornton et al. In View Of Zlotnick

Claims 61, 62, 76 and 77 were rejected as allegedly obvious from the combined teachings of Thornton et al. US Patent No. 5,143,726 (hereinafter Thornton) in view of Zlotnick as discussed above. The gist of this rejection is that Thornton teaches that one can link one can link a glycosylated peptide to HBc and thereby obtain a claimed construct with the help of the already discredited Zlotnick teachings. This rejection is respectfully traversed.

As has bee pointed out previously, a Zlotnick construct has to be considerably rebuilt in order to approach a claimed construct. The Thornton constructs also have to be rebuilt. Although one might be able to come up with a construct

of the claims if he already knew about the claimed subject matter. However, there were no blaze marks in this forest of disclosures leading the way for a skilled worker. For example, there is nothing that requires that a C-terminally-truncated HBc molecule be used. Thornton's construct was full length. There is no teaching about whether one should use a Zlotnick construct such as CP149 that has the internal cysteines, but no C-terminal cysteine. Thornton used a construct with a C-terminal Cys, and all of the internal cysteines. Thornton teaches use of an amino acid side chain for linking to the saccharide. The claims require that the linker be a heterologous linker and that that linker be placed within the region of the immunogenic loop. Thornton meets neither of those requirements and the relied-on art provides no teaching that directs the skilled worker in that direction. This basis for rejection should therefore be withdrawn.

D. Provisional Double-Patenting Rejection

Claims 1-78 (exclusive of cancelled claims) were provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting in view of specified claims of co-pending application No. 10/732,862. It is noted that the enumerated application has no allowed claims at this time. However, to speed prosecution, a Terminal Disclaimer and its appropriate fee are enclosed over the recited application.

E. Inventorship Issue

Dr. David R. Milich has asserted that he is a co-inventor of the present application and of application Serial

No. 09/931,325. Counsel reviewed the matter and could not find a basis for naming Dr. Milich a co-inventor.

The undersigned hired an outside attorney, Mr. Talivaldis Cepuritis, to examine the matter both on behalf of Apovia, the assignee, and The Scripps Research Institute, Dr. Milich's employer at the time the present invention was made, to independently re-examine the matter. Mr. Cepuritis traveled from Chicago to San Diego and interviewed Drs. Birkett, Milich and G.B. Thornton, the Managing Director of Apovia, provided an opinion to Mr. Fitting for Scripps, the undersigned for Apovia and to Dr. Milich's counsel, Ms. Hamdan. Mr. Cepuritis found that Dr. Milich did not qualify as an inventor of either application. A copy of Mr. Cepuritis' Letter of Opinion is attached hereto as Exhibit 5, with its Appendix being Exhibit 5A.

F. New Art

Dr. Milich brought a new disclosure to the attention of counsel. That paper is provided herewith as Exhibit 6, and is noted on the enclosed Form PTO 1449. That paper is Chang et al. (1994) *J. Virol.*, **68(8):**5225-5231, hereinafter Chang. That Chang paper discloses several HBv constructs including full-length constructs and constructs C-terminally-truncated after HBc position 157 that also include the C-terminal two residues of HBc. That truncated construct is referred to as Δ157. Further constructs contained an inserted sequence from hepatitis B surface antigen inserted between residues 78 and 80. That latter construct is referred to as Δ157L. The paper also

discloses mixed constructs made from HBc molecules from different mammals.

The Chang constructs going so far into the C-terminal region of HBc would of necessity not be "self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell". As such, this disclosure dose little for the skilled worker.

C. Summary

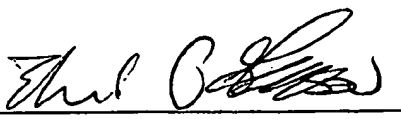
Claims 1, 18, 51, 63 and 75 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
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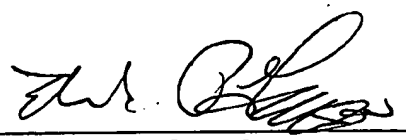
Enclosures
Exhibits 1 through 6.
Petition and fee
Terminal Disclaimer and fee

CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on January 25, 2005.

By 
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